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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/383, 978	08/26/99	SCHALLER	H BBI-102CP

000959
LAHIVE & COCKFIELD
28 STATE STREET
BOSTON MA 02109

HM22/1106

EXAMINER
NGUYEN, Q

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/06/01 B

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary	Application No.	Applicant(s)	
	09/383,978	SCHALLER ET AL.	
	Examiner	Art Unit	
	Quang Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 16 August 2001.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-8 and 33-50 is/are pending in the application.
 - 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-8 and 33-50 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All
 - b) Some *
 - c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 - a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendment filed August 16, 2001 in Paper No. 11 has been entered.

Claims 1-8 and 33-50 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Regretfully, Upon reconsideration of the present application, following is a new ground of rejection.

Claim Objections

Claims 3, 37, 41 objected to because of the following informalities: Misspellings are in the claims. Appropriate correction is required.

Claims 2, 34, 44 and 50 are objected to because of the following informalities: A period is missing at the end of every claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 33-41 and 49-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

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such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the *invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

Applicant's invention is drawn to methods of producing replication defective hepadnavirus particles at a titer suitable for infecting hepatocytes and for expressing a heterologous gene in hepatocytes using the same replication defective hepadnavirus particles, wherein a region of the preS or S-gene in the genome of said replication defective hepadnavirus particles has been replaced with a heterologous gene. The invention is also directed to the same replication defective hepadnavirus particles and a pharmaceutical composition comprising the same. The instant claims are not limited to replication defective hepadnavirus particles derived from human hepatitis B virus (HBV) or other HBVs known in the art at the effective filing date of the present application (see instant specification, page 11, lines 16-29). The breadth of the instant claims encompasses replication defective hepadnavirus particles derived from any naturally occurring small enveloped DNA-virus utilizing a reverse transcription pathway and

without requiring integration into the host genome for its genome replication (a characteristic of the hepadnaviridae family of viruses, see instant specification on page 2, lines 3-5), including those whose genomes have not yet been identified, isolated and characterized and/or those infecting human organs and cells such as exocrine and endocrine cells, tubular epithelium of the kidney, spleen cells, leukocytes, lymphocytes (see instant specification page 11, lines 23-28). Apart from the disclosure for preparing recombinant replication defective duck hepatitis B virus particles (rDHBV) and recombinant replication defective human hepatitis B virus particles (rHBV) which are species and hepatocyte specific, the instant specification fails to teach a sufficient representative numbers of replication defective hepadnavirus particles as encompassed by the scope of the instant claims. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of any replication defective hepadnavirus particles apart from those derived from hepatitis B virus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and

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reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

Claims 1, 37-38 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expressing a heterologous gene in hepatocytes *in culture* comprising:

providing replication defective hepatitis B virus particles at a titer level competent to infect hepatocytes, wherein an S-gene in the genome of said hepatitis B virus particles has been replaced with the heterologous gene of up to 800 nucleotides in length such that expression of the heterologous gene is regulated by an S-promoter; and

infecting hepatocytes with said hepatitis B virus particles such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes; does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a method for expressing a heterologous gene in hepatocytes comprising: providing replication defective hepadnavirus particles at a titre level competent to infect hepatocytes, wherein a region of the preS or S-gene of the hepadnavirus genome has been replaced with the heterologous gene such that expression of the heterologous gene is regulated by regulatory sequences of the preS or S-gene; and infecting hepatocytes with the hepadnavirus such that the heterologous gene is delivered into the hepatocytes and expressed in the hepatocytes. Claims 37-38 are drawn to a pharmaceutical composition comprising: a replication defective hepadnavirus with a region of its pre-S-genes deleted and replaced with a heterologous gene such that the sequences of the RC or RII that are essential for producing reverse transcriptase are retained, and a pharmaceutically acceptable carrier; the same further comprising a helper virus. Claim 42 is directed to a method for producing replication defective recombinant hepadnavirus particles capable of expressing a heterologous gene in hepatocytes.

The specification teaches the preparation and production of recombinant replication defective duck and human hepatitis B virus (rDHBV and rHBV, respectively) stocks. The specification further discloses that an efficient transfer and stable expression of the marker GFP gene operably linked to DHBV S-promoter could be established for viable cultured hepatocytes. In addition, the delivery of a transgene mediated by rDHBV has been shown to be both hepatocyte and species-specific as

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shown by the lack of GFP expression in non-parenchymal cells, primarily sinusoidal endothelial cells and Kupffer cells constituting about 15% of the total cell population in the primary hepatocyte cultures, and in primary mouse hepatocytes. Moreover, intravenous injection of rDHBV-GFP in ducklings resulted in the recovery of GFP-fluorescent hepatocytes 7 days post infection, indicating a successful *in vivo* gene transfer mediated by rDHBV-GFP. The specification further teaches that rDHBV can superinfect DHPV-infected cultured hepatocytes, but the transduction efficiency is 20-fold lower compared to hepatocyte cultures not preinfected with DHBV. Additionally, superinfection of cultured DHPV-infected hepatocytes with rDHBV-IFN resulted in a decrease in DHBV production relative to untreated controls, indicating that the inhibition was caused by the expression of transduced IFN transgene. Similarly, human rHBV was shown to infect cultured primary human hepatocytes comparable to wild type HBV, and that the delivery of a transgene mediated by rHBV is species and hepatocyte-specific *in vitro*.

The above evidence has been noted and considered. However, the evidence can not be reasonably extrapolated to the instant broadly claimed invention. With respect to claims 1 and 42, they encompass both *in vitro* and *in vivo* methods for expressing a heterologous gene in hepatocytes. When read in light of the specification, the sole purpose for the *in vivo* methods as claimed is for providing an effective level of a therapeutic gene product, preferably a cytokine, more preferably IFN α , TNF α , IFN β , IL-18 and IFN γ , to treat a subject having a hepatic disorder or hepatitis infection. Similarly, when read in light of the specification a pharmaceutical composition

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comprising replication defective recombinant hepadnavirus particles of the present invention is for treating a subject having a hepatic disorder or a hepatitis infection. As enablement requires the specification to teach how to *make and use* the claimed invention, the instant specification fails to enable the use of the instant broadly claimed invention for the reasons discussed below.

The specification is not enabled for the **use** of the instantly claimed invention because at the effective filing date of the present application, the art of gene therapy was still considered to be highly unpredictable and immature. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted several known factors limiting the effectiveness of gene therapy and these include the lack of optimal vectors, host immunological responses to the vectors, the lack of long term and stable transgene expression *in vivo*, as well as an efficient transgene delivery to target tissues (page 474, column 2, lines 4-9 of the last paragraph). Dang et al. further stated that "This work shop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement **to make gene therapy a reality**" (page 471, column 1, last sentence of first paragraph). The instant specification fails to provide sufficient guidance or direction regarding to the use of any replication defective recombinant hepadnavirus particles to achieve any therapeutic effects contemplated by Applicants. The specification fails to provide a nexus between the expression of a marker gene GFP in hepatocytes *in vivo* and the desired therapeutic results for treating a subject having a hepatic disorder or a hepatitis infection using the replication defective recombinant hepadnavirus of the

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present invention. Since the prior art at the time the invention was made does not provide such teachings, it is incumbent upon the present specification to do so. Even a year after the effective filing date of the present application, the only therapy for chronic hepatitis that has a lasting beneficial effect is systemic treatment with IFN- α (Protzer et al., Proc. Natl. Acad. Sci. 96:10818-10823; 1999; IDS). Given the apparently low *in vivo* transduction rates reported in this application (1 GFP-positive cell per 10^4 to 10^5 hepatocytes and at least 20-time less efficient for preinfected hepatocytes for the rHBV particles), the instant specification fails to demonstrate that at such low transduction rates a substantial portion of a recipient liver could be infected by the recombinant hepadnavirus of the presently claimed invention to yield any beneficial effects. Nor does it provide specific teachings for optimizing or improving conditions (dosage used, route of delivery, recombinant vector constructs) to achieve an effective transduction rate in the targeted cells to obtain therapeutic results contemplated by Applicants. It should be further noted that adverse host immune responses reactive against administering recombinant hepadnavirus particles may further reduce the effectiveness of transgene delivery to intended targeted cells as well as the unpredictability of *in vivo* vector targeting known in the art. Moreover, with respect to the breadth of the instant claims encompassing any heterologous gene, it is uncertain whether an effective level and stable expression of any therapeutic gene in targeted cells could be achieved *in vivo* to yield the desired therapeutic effects. Eck & Wilson (Gene-based therapy, PTO-892 in paper no. 7) noted that several factors such as the level of mRNA produced, the stability of the protein generated, the protein's proper compartmentalization within the

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cell or its secretory fate differ dramatically based on which protein being produced (page 81, column 2 continues to page 82). Therefore, the level of transgene expression, its duration and its *in vivo* therapeutic effect sought to achieve are not always predictable nor can they be overcome with routine experimentation. Due to the lack of guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

The broad claims encompass any recombinant replication defective hepadnavirus particles, and not necessarily limited to replication defective hepadnavirus particles derived from human hepatitis B virus (HBV) or other HBVs known in the art at the effective filing date of the present application (see instant specification, page 11, lines 16-29). They encompasses replication defective hepadnavirus particles derived from any naturally occurring small enveloped DNA-virus utilizing a reverse transcription pathway and without requiring integration into the host genome for its genome replication (a characteristic of the hepadnaviridae family of viruses, see instant specification on page 2, lines 3-5), including those whose genomes have not yet been identified, isolated and characterized and/or those infecting human organs and cells such as exocrine and endocrine cells, tubular epithelium of the kidney, spleen cells, leukocytes, lymphocytes (see instant specification page 11, lines 23-28). The instant specification is not enabled for such a broadly claimed invention for the reasons already stated in the lack of Written Description Section above.

The instant claims also encompass the replacement of a region of the preS or S-gene with a heterologous gene of any length. It is noted that the term a "region" of a

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gene refers to the length of nucleotide sequence of the hepadnavirus genome which is replaced by a heterologous gene not necessarily limited to any particular length (see instant specification, page 12, lines 8-13). The instant specification is not enabled for such a broadly claimed invention. This is because apart from the exemplification of rDHBV and rHBV particles, the instant specification fails to provide sufficient guidance for a skilled artisan on how to generate high titers of replication defective recombinant hepadnavirus particles containing any heterologous gene larger than 800 nucleotides in length to infect hepatocytes and for expressing said heterologous gene. For example, the specification fails to teach specifically which cis-acting control elements, internal promoters or enhancers and in which combinations should be maintained in order to achieve at least the titers obtained for rDHBV and rHBV particles, and which genomic segments to be deleted or replaced so as to increase the size of incorporated heterologous gene. Protzer et al. (Proc. Natl. Acad. Sci. 96:10818-10823; 1999; IDS) stated that "Despite these precautions (with respect to care taken not to exceed the authentic genome size and not to affect cis-acting control elements), among the several constructs in which different genome segments were replaced, only substitution of the small envelope (S) gene by foreign sequences turned out to be successful" (page 40820, col. 2, bottom of first paragraph). Therefore, with the lack of sufficient guidance of the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

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With regard to the breadth of the instant claims, particularly with respect to any replication defective recombinant hepadnavirus particles, Applicants' attention is further directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; *In re Wahlforss et al.*, 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Additionally, the courts have also stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in the patent application (27 USPQ2d 1662 *Ex parte Maizel*.).

Accordingly, due to the lack of guidance provided by the specification regarding to the aforementioned issues, the amount of experimentation necessary, the unpredictability of the gene therapy, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claims 2-8, 33-41 and 43-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cultured method of producing replication defective hepatitis B virus particles at a titer level competent to infect hepatocytes, wherein an S-gene in the genome of said hepatitis B virus particles has been replaced with the heterologous gene of up to 800 nucleotides in length such that expression of the heterologous gene is regulated by an S-promoter; the same

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replication defective hepatitis B virus particle and its recombinant genome; does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 39, 41 and 3-8 are directed to a method of producing replication defective hepadnavirus particles at a titer suitable for infecting hepatocytes comprising: co-transfected hepatocyte cells of a hepatoma cell line with (i) replication defective hepadnavirus constructs, wherein a region of one of a pre S or an S-gene of the hepadnavirus DNA has been replaced with a gene encoding a heterologous gene while retaining one of an RC or RII signal, such that the expression of the gene encoding a cytokine is regulated by regulatory sequences of the S-gene; and (ii) a helper construct for transcomplementing lacking viral gene products; culturing the hepatocytes until infectious viral particles are produced; and recovering the infectious particles.

Claims 33-36 and 49-50 are directed to a replication defective hepadnavirus particle, wherein a region of a pre-S and S-gene of the hepadnavirus genome have been deleted and replaced by a heterologous gene such that the sequences for RC and RII that are essential for producing reverse transcriptase are retained.

Claims 43-48 are directed to a recombinant HBV genome, wherein an S-gene in the HBV genome is deleted and replaced by a heterologous gene and wherein the sequences for RC and RII that are essential for reverse transcription are retained.

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The specification is not enabled for the instant broadly claimed invention for the same reasons already set forth in the lack of Written Description and in the rejection of claims 1, 37-38 and 42 above. With the lack of guidance provided by the instant disclosure, it would have required undue experimentation for a skilled artisan to make and use the instant broadly claimed invention.

Response to Arguments

It is noted that Applicants' arguments in the Amendment filed on August 16, 2001 in Paper No. 11 (pages 14-15) are not relevant to the rejections set forth above.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-8 and 33-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 2-8, 33-39, 41 and 43-50, it is unclear what is encompassed by the phrases "an RC or RII signal", "the sequences of the RC r RII", "the sequences for RC and RII" and "the sequences for RC and RII" for independent claims 39, 37, 33 and 43, respectively. What are the abbreviations of RC or RII stand for? Since these terms are not clearly defined in the instant specification, nor Applicants clearly point out where in

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the specification (page and line numbers, please) the definition of these terms can be found, the metes and bounds of the claims can not be clearly determined.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 39 recites the broad recitation "a heterologous gene" and the claim also recites "such that the expression of the gene encoding a cytokine" which is the narrower statement of the range/limitation.

Similarly, claim 42 recites the broad recitation for "producing replication defective recombinant hepadnavirus particles" and the claim also recites "replacing an S-gene in a hepatitis B virus genome" which is the narrower statement of the range/limitation.

Claim 40 is indefinite because it is dependent on the cancelled claim 9. Therefore, the metes and bounds of the claim can not be clearly determined.

Conclusions

Claims 1-8 and 33-50 are free of prior art. The prior art did not teach or fairly suggest the presently claimed invention.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Karen Hauda, at (703) 305-6608.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Patsy Zimmerman, whose telephone number is (703) 308-0009.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1632.

Quang Nguyen, Ph.D.



DAVE T. NGUYEN
PRIMARY EXAMINER